

PCT / IN 04 / 00133



INTELLECTUAL
PROPERTY **INDIA**
PATENTS / DESIGNS / TRADE MARKS /
GEOGRAPHICAL INDICATION



सत्यमेव जयते

Government Of India
Patent Office
Todi Estates, 3rd Floor,
Lower Parel (West)
Mumbai - 400 013

REC'D 30 SEP 2004

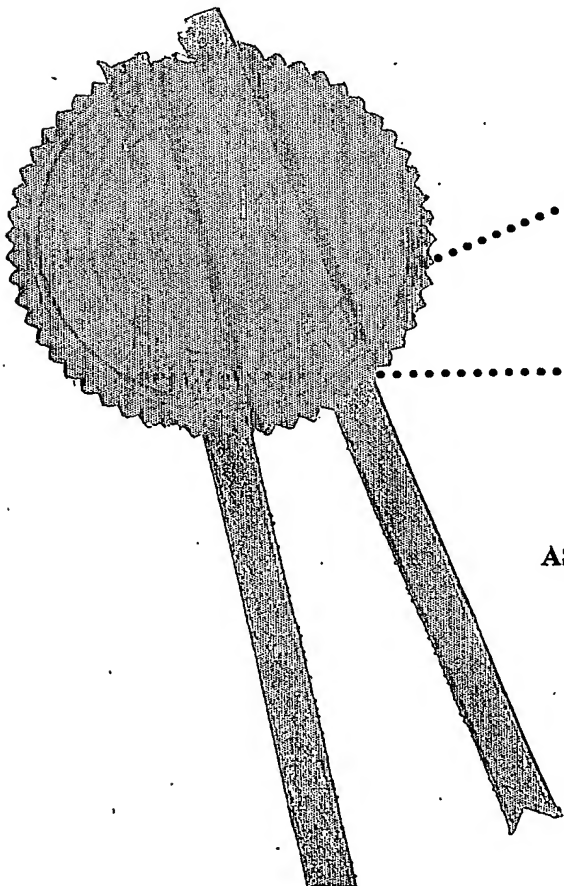
WIPO

PCT

THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of
Application and Complete Specification filed on 05/06/2003 in respect of Patent Application
No. 504/MUM/2002 of M/S. ALEMBIC LIMITED, ALEMBIC ROAD, VADODARA - 390
003, GUJARAT, INDIA, An Indian Company incorporated under the Companies Act, 1956.

This certificate is issued under the powers vested in me under
Section 147 (1) of the Patents Act, 1970.



.....
Dated this 30th day of Sept 2004.


(R. BHATTACHARYA)

ASST. CONTROLLER OF PATENTS & DESIGNS.

**PRIORITY
DOCUMENT**

SUBMITTED OR TRANSMITTED IN
COMPLIANCE WITH RULE 17.1(a) OR (b)

BEST AVAILABLE COPY

FORM 1
THE PATENTS ACT, 1970
(39 of 70)
APPLICATION FOR GRANT OF A PATENT
(See section 7)

1. We
- a) M/s. ALEMBIC LIMITED,
 - b) ALEMBIC ROAD, VADODARA - 390 003, GUJARAT, INDIA,
 - c) An Indian Company incorporated under the Companies Act, 1956
2. Hereby declare:
- a) that we are in possession of an invention titled "A PROCESS OF PREPARING EXTENDED RELEASE OSMO MICROSEALED VENLAFAXINE HYDROCHLORIDE TABLETS".
 - b) That the Complete specification relating to this invention is filed with this application.
 - c) That there is no lawful ground of objection to the grant of a patent to us.
3. Further declare that the inventors for the said invention are :
- i)
 - a) BHATTACHARYA SAMPAD,
 - b) C/o ALEMBIC LIMITED, ALEMBIC ROAD, VADODARA - 390 003, GUJARAT, INDIA,
 - c) An Indian National
 - ii)
 - a) GUMMUDAVELLI SRIDHAR
 - b) C/o ALEMBIC LIMITED, ALEMBIC ROAD, VADODARA - 390 003, GUJARAT, INDIA,
 - c) An Indian National
 - iii)
 - a) JOSHI MAYANK
 - b) C/o ALEMBIC LIMITED, ALEMBIC ROAD, VADODARA - 390 003, GUJARAT, INDIA,
 - c) An Indian National
4. That we are the assignees of the true and first inventors.
5. That our address for service in India is as follows:
- M/s. Ramu & Associates,**
253 Shantivan Co-op. Hsg. Soc. Ltd., New Link Road Extn., Andheri (W),
Mumbai - 400 053, Maharashtra, India,
Tel No: 91-22-26327650 Fax No: 91-22-26302201

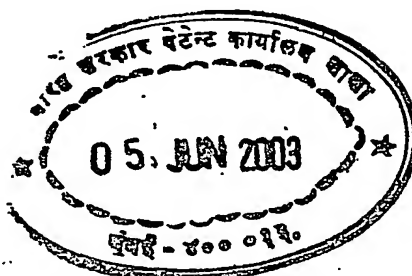
DRGN

504/M/2002

The application has been
Post dated to 05.06.2003
u/s, 9(4) of Patent Act.

(M. Ramchander)

Examiner of Patents & Designs.



Contd. 2

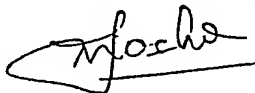
6. Following declaration was given by the inventors : We the true and the first inventors for this invention declare that the applicants herein are our assignees.



Shri Sampad Bhattacharya



Mr. Sridhar Guimudavelli



Dr. Mayank Joshi

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Following are the attachment with the application :

- (a) Provisional Specification (3 copies)
- (b) Statement and Undertaking on FORM-3
- (c) Fee Rs. 5000 by Cash

We request that a Patent may be granted to us for the said invention.

Dated this 6th day of June , 2002

For M/s. ALEMBIC LIMITED



(Shri Sampad Bhattacharya)
Vice President - Technical

To,
The Controller of Patents
Patent office branch,
Mumbai.



COMPLETE AFTER PROVISIONAL
EFT OFF 5 JUN 2003

THE PATENTS ACT, 1970
(39 of 1970)

COMPLETE SPECIFICATION
(See Section 10)

A PROCESS OF PREPARING EXTENDED RELEASE OSMO MICROSEALED
VENLAFAXINE HYDROCHLORIDE TABLETS

M/S. ALEMBIC LIMITED, ALEMBIC ROAD, VADODARA - 390 003, GUJARAT, an Indian
Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention, and
the manner in which it is to be performed.

-1-



DUPLICATE
504/MUM/2002

This invention relates to "A process of preparing extended release osmo microsealed venlafaxine hydrochloride tablets".

Venlafaxine hydrochloride is a structurally novel oral antidepressant. It is chemically unrelated to other antidepressants like tricyclic, tetracyclic and other available antidepressant agents.

Venlafaxine hydrochloride is available in both conventional and extended release capsule dosage forms.

The present invention relates to an Osmo-Microsealed Venlafaxine particles in hydrophilic matrix, it pertains to Osmo-Microsealed Venlafaxine 24 hr extended release dosage form, which provides better control of blood plasma levels than conventional tablet formulations which must be administered two or more times a day and further provides a lower incidence of nausea and vomiting than the conventional tablets.

The main advantage of the invention is:

1. Easy to manufacture in comparison with Extended release capsules.
2. Venlafaxine being highly water soluble drug, conventional hydrophilic matrix systems necessitates a very high polymer levels. Therefore the coating of venlafaxine hydrochloride provided in the present invention provides for an efficient modulation of the system for desired drug release.
3. A combination of water insoluble and water swellable polymer helps to achieve the desired drug levels in plasma.
4. The presence of osmotic agent in the micro sealed systems enables a driving force for water to penetrate into the system and thereby ensures complete drug release from water insoluble polymer coated micro particle.
5. By altering the level of osmogen the desired release profile from the micro osmotic system can be achieved.
6. The external hydrophilic matrix base enables the regulated loading of individual micro osmotic particles of venlafaxine hydrochloride in the GIT.
7. Water insoluble polymer surrounding the drug osmogen mixture prevents dose dumping at any instance.
8. The osmo microsealed device enables a higher gastric residence time.

Accordingly the invention provides a process of preparing extended release osmo microsealed Venlafaxine Hydrochloride tablets comprising of the following steps,

- a. Dry blending Venlafaxine Hydrochloride 1 to 68% by wt., Microcrystalline cellulose 1 to 60% by wt., Lactose 0.15 to 60% by wt., and Povidone 0.1 to 25% by wt.,
- b. Granulating the blended mixture of step (a) with the solution of Sodium Chloride from 0.001 to 25% by wt.,
- c. Continuing the granulation process of step (b) with aqueous dispersion of ethyl cellulose 0.5 to 55% by wt., forming the inner inner osmo microsealed particulate phase,
- d. Drying the said inner osmo microsealed particulate phase of step (c) in a suitable drier,

- e. Lubricating the dried inner osmo microsealed particulate phase of step (d) with Hydroxypropyl Methylcellulose 1 to 98% by wt., Talc 0.001 to 5% by wt., and Magnesium stearate from 0.001 to 5% by wt. forming outer continuous phase,
- f. Compressing the tablets of suitable shape from the lubricated mass of step (e),
- g. Coating the said tablets of step (f) with an aqueous dispersion of Ammonio Methacrylate Copolymer 1 to 15% by wt. containing talc, titanium, triethyl citrate and suitable color,

The invention will now be clearly described in the following examples.

The process of preparing a process of preparing extended release osmo microsealed venlafaxine hydrochloride tablets comprises the following steps:

EXAMPLE 1:

1. Sift Venlafaxine hydrochloride, Microcrystalline cellulose, lactose and povidone through #60 using a turbosifter.
2. Dry blend the sifted mass of step (1) in a Disona type high shear mixture.
3. Granulate the blended mixture of step (2) with the solution of sodium chloride.
4. Dry the granules of step (3) in Tray drier at 55-60°C until moisture content comes down to 2.0-2.2% w/w.
5. Continue granulation with the aqueous dispersion of ethyl cellulose.
6. Dry the granules of step (5) in oven at 55-60°C until moisture content comes down to 2.0-2.2% w/w.
7. Repeat the process of step (5) and (6) till complete loading of ethyl cellulose is achieved.
8. Pass the dried granules of step (7) through # 20.
9. Lubricate the sized granules of step (8) with Hydroxypropyl methylcellulose, Magnesium Stearate and Talc sifted through # 40 sieve.
10. Compress the lubricated blend of step (9) into tablets of an appropriate shape.
11. Load the core tablets of step (10) into a pear shaped coating pan and de-dust by jogging the pan.
12. Coat the tablets with a aqueous dispersion of Ammonio Methacrylate Copolymer containing Talc, Titanium dioxide, Triethyl Citrate and Quinoline yellow (lake).

The Venlafaxine hydrochloride 150 mg Osmo Microsealed Extended Release Tablets comprises the following ingredients:

S.No.	Ingredients	mg / tablet
INNER OSMO MICROSEALED PARTICULATE PHASE		
1.	Venlafaxine Hydrochloride	171.00
2.	Lactose	66.00
3.	Microcrystalline Cellulose	190.00
4.	Povidone	15.00
5.	Sodium Chloride	25.00
6.	Aqueous ethyl cellulose dispersion (Solid Content)	107.50
OUTER CONTINUOUS PHASE		
7.	Hydroxypropylmethyl cellulose	275.00
8.	Purified Talc	5.50
9.	Magnesium stearate	10.00
FUNCTIONAL COATING		
10.	Ammonio methacrylate copolymer (Solid content)	21.00
11.	Talc	4.00
12.	Titanium dioxide	4.75
13.	Triethyl citrate	5.00
14.	Quinoline Yellow (lake)	0.25
	Total	900.00
15.	Ammonium Hydroxide 28 %	Lost in processing
16.	Water	Lost in processing

EXAMPLE 2:

1. Sift Venlafaxine hydrochloride, Microcrystalline cellulose, lactose and povidone through #60 using a turbosifter.
2. Dry blend the sifted mass of step (1) in a Diasona type high shear mixture.
3. Granulate the blended mixture of step (2) with the solution of sodium chloride.
4. Continue granulation with the aqueous dispersion of ethyl cellulose.
5. Dry the granules of step (4) in Tray drier at 55-60°C until moisture content comes down to 2.0-2.2% w/w.

6. Pass the dried granules of step (5) through # 20 .
7. Lubricate the sized granules of step (6) with Hydroxypropyl methylcellulose, Magnesium Stearate and Talc sifted through # 40 sieve.
8. Compress the lubricated blend of step (7) into tablets of an appropriate shape.
9. Load the core tablets of step (8) into a pear shaped coating pan and de-dust by jogging the pan.
10. Coat the tablets with a aqueous dispersion of Ammonio Methacrylate Copolymer containing Talc, Titanium dioxide, Triethyl Citrate and Quinoline yellow (lake).

The Venlafaxine hydrochloride 150 mg Osmo Microsealed Extended Release Tablets comprises the following ingredients:

S.No.	Ingredients	mg / tablet
INNER OSMO MICROSEALED PARTICULATE PHASE		
1.	Venlafaxine Hydrochloride	171.00
2.	Lactose	27.00
3.	Microcrystalline Cellulose	216.00
4.	Povidone	25.00
5.	Sodium Chloride	15.00
6.	Aqueous ethyl cellulose dispersion (Solid Content)	27.50
OUTER CONTINUOUS PHASE		
7.	Hydroxypropylmethyl cellulose	345.00
8.	Purified Talc	5.50
9.	Magnesium stearate	10.00
FUNCTIONAL COATING		
10.	Ammonio methacrylate copolymer (Solid content)	35.00
11.	Talc	7.00
12.	Titanium dioxide	9.00
13.	Triethyl citrate	6.50
14.	Quinoline Yellow (lake)	0.50
	Total	900.00
15.	Ammonium Hydroxide 28 %	Lost in processing
16.	Water	Lost in processing

EXAMPLE 3:

1. Sift Venlafaxine hydrochloride, Microcrystalline cellulose, lactose and povidone through #60 using a turbosifter.
2. Dry blend the sifted mass of step (1) in a Disona type high shear mixture.
3. Granulate the blended mixture of step (2) with the solution of sodium chloride.
4. Dry the granules of step (3) in oven at 55-60°C until moisture content comes down to 2.0-2.2% w/w.
5. Continue granulation with the aqueous dispersion of ethyl cellulose.
6. Dry the granules of step (5) in Fluid Bed drier at 55-60°C until moisture content comes down to 2.0-2.2% w/w.
7. Repeat the process of step (5) and (6) till complete loading of ethyl cellulose is achieved.
8. Pass the dried granules of step (7) through # 20 .
9. Lubricate the sized granules of step (8) with Hydroxypropyl methylcellulose, Magnesium Stearate and Talc sifted through # 40 sieve.
10. Compress the lubricated blend of step (9) into tablets of an appropriate shape.
11. Load the core tablets of step (10) into a pear shaped coating pan and de-dust by jogging the pan.
12. Coat the tablets with a aqueous dispersion of Ammonio Methacrylate Copolymer containing Talc, Titanium dioxide and Triethyl Citrate.

**The Venlafaxine hydrochloride 37.5 mg Osmo Microsealed Extended Release Tablets
Comprises The Following Ingredients :**

S.No.	Ingredients	mg / tablet
	INNER OSMO MICROSEALED PARTICULATE PHASE	
1.	Venlafaxine Hydrochloride	42.75
2.	Lactose	108.25
3.	Microcrystalline Cellulose	67.00
4.	Povidone	15.00
5.	Sodium Chloride	5.00
6.	Aqueous ethyl cellulose dispersion (Solid Content)	19.00

	OUTER CONTINOUS PHASE	
7.	Hydroxypropylmethyl cellulose	142.00
8.	Purified Talc	4.00
9.	Magnesium stearate	6.00
	FUNCTIONAL COATING	
10.	Ammonio methacrylate copolymer (Solid content)	16.00
11.	Talc	3.00
12.	Titanium dioxide	4.00
13.	Triethyl citrate	3.00
	Total	435.00
14.	Ammonium Hydroxide 28 %	Lost in processing
15.	Water	Lost in processing

The above description and illustrations in the examples are given to understand the invention rather than to limit its scope

We claim

1. A process of preparing extended release osmo microsealed Venlafaxine Hydrochloride tablets comprising of the following steps,
 - a. dry blending Venlafaxine Hydrochloride 1 to 68% by wt., Microcrystalline cellulose 1 to 60% by wt., Lactose 0.15 to 60% by wt., and Povidone 0.1 to 25% by wt.;
 - b. granulating the blended mixture of step (a) with the solution of Sodium Chloride from 0.001 to 25% by wt.;
 - c. continuing the granulation process of step (b) with aqueous dispersion of ethyl cellulose 0.5 to 55% by wt., forming the inner osmo microsealed particulate phase;
 - d. drying the said inner osmo microsealed particulate phase of step (c) in a suitable drier.
 - e. lubricating the dried inner osmo microsealed particulate phase of step (d) with Hydroxypropyl Methylcellulose 1 to 98% by wt., Talc 0.001 to 5% by wt., and Magnesium stearate from 0.001 to 5% by wt. forming outer continuous phase;
 - f. compressing the tablets of suitable shape from the lubricated mass of step (e);
 - g. coating the said tablets of step (f) with an aqueous dispersion of Ammonio Methacrylate Copolymer 1 to 15% by wt. containing talc, titanium, triethyl citrate and suitable color.
2. A process as claimed in claim 1 wherein the said inner osmo microsealed particulate phase and the outer continuous phase is in a ratio within the range of 0.01 : 1 to 4 : 1, preferably from 0.3 : 1 to about 2 : 1.
3. A process as claimed in claim 1, wherein the inner osmo microsealed phase contain the drug Venlafaxine Hydrochloride from about 5 % to 55 % by weight, the solid content of ethyl cellulose aqueous dispersion from 1 % to 35 % by weight, microcrystalline cellulose in an amount within the range from 5 % to 50 % by weight, Lactose in an amount from 5 % to 50 % by weight, povidone in the range from 0.5 % to 10 % by weight, and sodium chloride from 0.002 % to 5 % by weight the above percentage being based on the weight of the inner osmo microsealed particulate phase.
4. A process as claimed in claim 1, wherein the said outer continuous phase contains Hydroxypropyl Methylcellulose from 5 % to 60 % by weight, Talc from 0.5 % to 2 % by weight, Magnesium stearate from 0.5 % to 2 % by weight, the above percentages being based on the weight of the core Tablet.
5. A process as claimed in claim 1, wherein the coating dispersion of the tablet in addition to Ammonio Methacrylate Copolymer contains Talc as a glidant, Titanium dioxide as opacifying agent, Triethyl citrate as plasticizer and suitable color, from about 1 to 15 % by weight of the tablet composition in addition.
6. A process claimed in claim 1, wherein the aqueous ethyl cellulose dispersion contains ethyl cellulose additives such as Oleic acid, Cetyl alcohol, Medium chain triglycerides, Ammonium Hydroxide 28%, Sodium lauryl sulphate and Dimethylpolysiloxane.

7. A process as claimed in claim 1, wherein the said Venlafaxine Hydrochloride, Cellulose, Lactose and Providedone are shifted through #60 using a turbo shifter before dry blending.
8. A process as claimed in claim 1, wherein the inner osmo microsealed particulate phase granules are dried in a tray dryer of temperature 55 to 60° C and the dried granules are passed through #20.-
9. A process as claimed in claim 1, wherein the dried granules of inner osmo microsealed particulate phase are granulated with the dispersion of ethyl cellulose to acquire the necessary loading of ethyl cellulose.
10. A Process of Preparing Extended Release Osmo Microsealed Venlafaxine Hydrochloride Tablets substantially as herein described and illustrated in Example 1 to 3 of this specification and the examples 1 to 3 of the provisional specification.

Dated this 6th day of June, 2002.



(V RAMU)
Agent for the applicant

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

☐ **BLACK BORDERS**

☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**

☐ **FADED TEXT OR DRAWING**

☒ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**

☐ **SKEWED/SLANTED IMAGES**

☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**

☐ **GRAY SCALE DOCUMENTS**

☒ **LINES OR MARKS ON ORIGINAL DOCUMENT**

☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**

☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.